



BACKGROUND

- Intrathecal (IT) opioids are an efficacious and widely used modality to treat postoperative pain after colorectal surgery
- (IT) opioids confer superior postoperative analgesia to systemic opioids as they deliver analgesia directly to their site of action while curtailing the undesired side effects of the parenteral route.
- While morphine has been established as the “gold” standard, hydromorphone has gained popularity as an alternative
- A prospective trial in women undergoing Cesarean delivery showed optimal dose doses to be 150 mcg for IT morphine and 75 mcg for IT hydromorphone

In colorectal surgery, clinical dosing of neither IT morphine nor hydromorphone is based on anecdotal evidence and retrospective studies and the optimal dose for neither agent has been established in a randomized prospective trial.

OBJECTIVES

- Determine the optimal dose expressed as ED₉₀ for IT morphine and hydromorphone in patients undergoing minimally invasive colorectal surgery
- Assess overall quality of recovery and presence of opioid side effects across the entire` dose range for both agents

METHODS

- Double-blinded prospective trial (NCT04752033)
- Patients who met the inclusion criteria randomized into either morphine or hydromorphone arm
- ED₉₀ was defined a dose needed to achieve pain numerical rating scale (NRS) score ≤4 with postoperative opioid requirements ≤15 opioid morphine equivalent (OME) 12 hours after medication administration in 90% patients
- ED₉₀ for both drugs determined by a sequential up-and-down method using a biased coin design
- Dose range examined:
Morphine: 25 - 50 - 100 (starting dose) - 150 - 200 - 250 - 300 - 350 - 400 mcg
Hydromorphone: 10 - 25 - 50 (starting dose) - 75 - 100 - 125 - 150 - 175 - 200 mcg
- Secondary outcomes included NRS pain scores, Overall Benefits of Analgesia (OBAS), Quality of Recovery (QoR) 15, opioid consumption and side effects, presence of adverse events, and patient satisfaction for up to 48 hours
- All patients received a standardized regimen of multimodal analgesics and antiemetics

RESULTS

- A total of 80 patients completed the study with 40 patients in each treatment group (Table 1)
- ED₉₀ could not be determined for either drug due to consecutive analgesic failures (Figure 1)

- ED₅₀ was calculated instead and was 100 mcg (95% CI was below the lowest dose) for morphine and 75 mcg (95% CI 50–200 mcg) for hydromorphone.

TABLE 1: PATIENT CHARACTERISTICS

	Morphine (n=40)	Hydromorphone (n=40)	p-value
Age, median (IQR)	52.0 (40.5, 63.0)	52.5 (34.0, 66.0)	0.973
Gender, n (%)			0.263
Female	23 (58%)	18 (45%)	
Male	17 (43%)	22 (55%)	
BMI, median (IQR)	27.6 (25.2, 32.0)	28.4 (25.4, 31.7)	0.940
Race, n (%)			0.222
White	38 (95%)	39 (98%)	
African American	2 (5%)	0 (0%)	
Other	0 (0%)	1 (3%)	

IQR, interquartile range

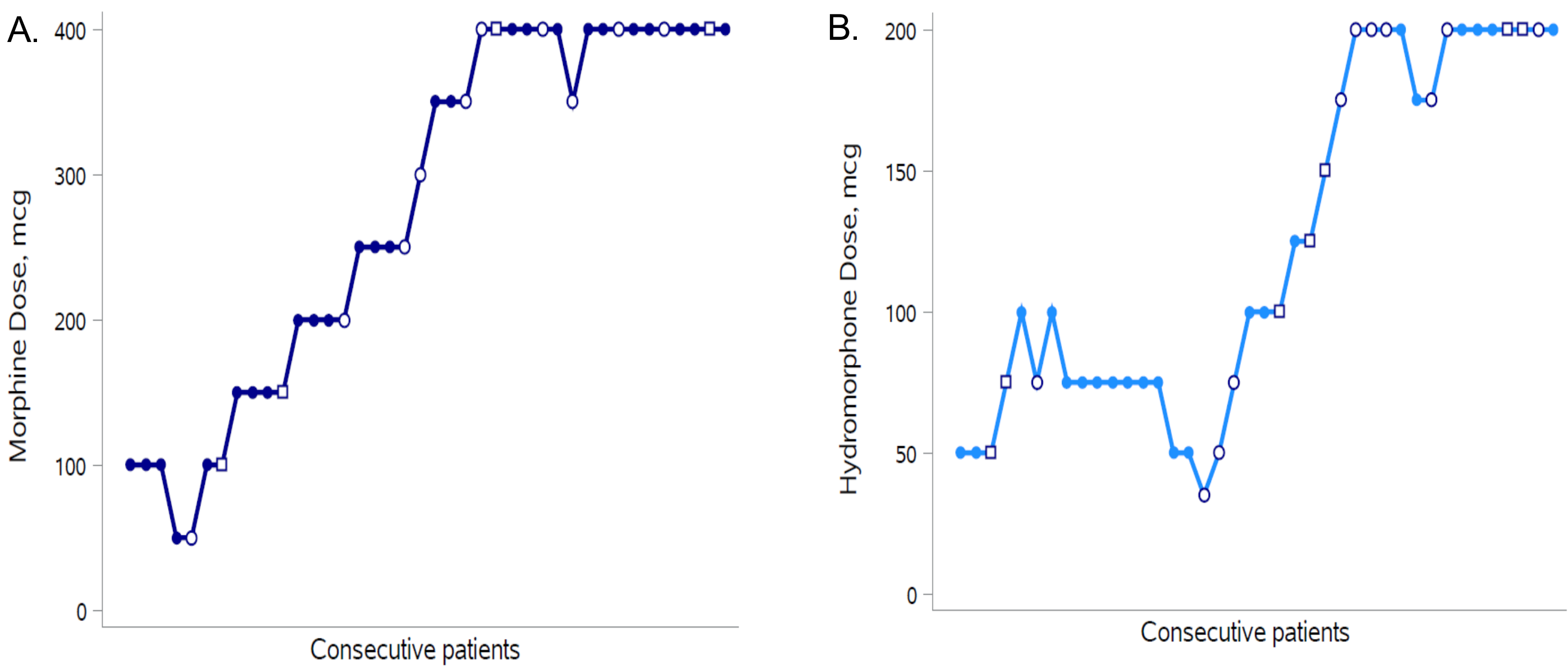
TABLE 2: CORRELATION BETWEEN SIDE EFFECTS AND DOSE ACROSS THE DOSING INTERVAL

	12 hours		24 hours	
	Correlation coefficient	p-value	Correlation coefficient	p-value
Morphine				
Nausea	0.027	0.866	-0.024	0.879
Pruritus	0.322	0.043*	0.233	0.147
OBAS	0.094	0.564	0.149	0.360
Hydro morphine				
Nausea	0.104	0.522	0.208	0.197
Pruritus	0.393	0.012*	0.390	0.013*
OBAS	0.084	0.605	-0.011	0.949

RESULTS

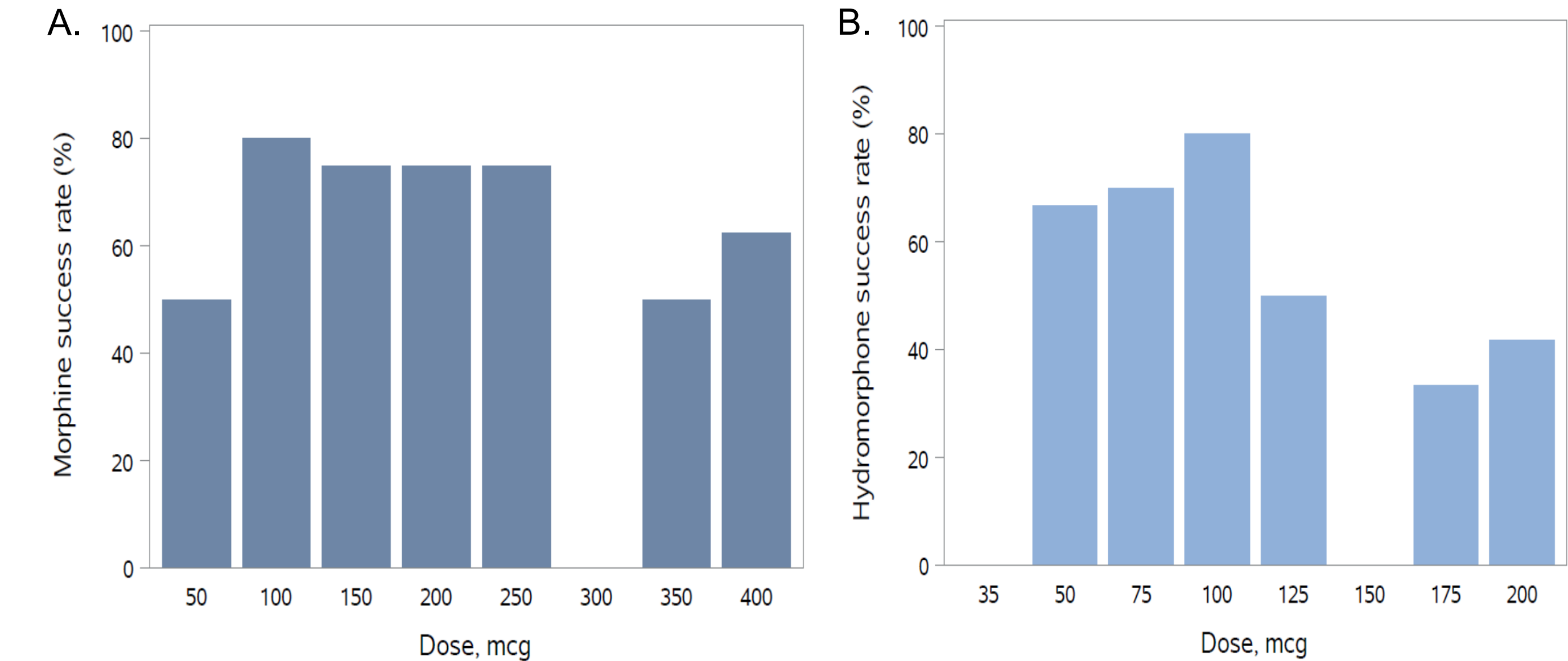
- While the failures resulted in an increase in the dose of both medications, most patients (65% for morphine and 55% for hydromorphone) met the criteria for success in terms of both NRS scores and OME requirements across the entire dose range (Figure 2).
- As the dose of hydromorphone increased, moderate to severe pruritus increased (P=0.009; Table 2)

FIGURE 1: SUMMARY OF UP-AND-DOWN BIASED COIN DOSE ALLCOATION FOR (A) MORPHINE AND (B) HYDROMORPHONE



Analgesic “successes” are represented by a filled circle. Analgesic “failures” are represented by an open circle for pain score > 4 and open square for total OME >15.

FIGURE 2: SUCCESS RATE PER DOSE FOR (A) MORPHINE AND (B) HYDROMORPHONE



DISCUSSION

- First double-blinded, prospective, dose-finding trial of IT opioids in patients undergoing colorectal surgery
- Inability to determine ED₉₀ attributed to:
 - ED₉₀ outside of the dose range
 - Procedure or population heterogeneity
 - Small magnitude of effect in the setting of multimodal analgesia
 - Inconsistent pattern of administration of PRN opioids
- Pruritus noted for both agents, with a statistically significant difference noted with dose escalation of hydromorphone

CONCLUSIONS

- ED₅₀ determined for both IT morphine and hydromorphone, and was 100 mcg and 75 mcg, respectively)
- High satisfaction for both agents across the entire dosing regimen with no observed serious adverse events

REFERENCES

- Merchea A, Lovely JK, Jacob AK, Colibaseanu DT, Kelley SR, Mathis KL, Spears GM, Huebner M, Larson DW: Efficacy and Outcomes of Intrathecal Analgesia as Part of an Enhanced Recovery Pathway in Colon and Rectal Surgical Patients. Surg Res Pract 2018; 2018:1–5
- Sviggum HP, Arendt KW, Jacob AK, Niesen AD, Johnson RL, Schroeder DR, Tien M, Mantilla CB: Intrathecal Hydromorphone and Morphine for Postcesarean Delivery Analgesia: Determination of the ED 90 Using a Sequential Allocation Biased-Coin Method. Anesth Analg 2016; 123:691–7
- Pace NL, Stylianou MP: Advances in and Limitations of Up-and-down Methodology. Anesthesiology 2007; 107:144–52